COE Loss-of-Function Analysis Reveals a Genetic Program Underlying Maintenance and Regeneration of the Nervous System in Planarians.

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Public Summary:
COE transcription factors are conserved across divergent animals and are important for development. COE genes are also functional in adult animals and have been implicated in central nervous system (CNS) diseases; however, the function of COE in the adult CNS remains poorly understood. Planarian regeneration provides an excellent model to study the function of transcription factors in cell differentiation and in mature cells. In planarians, coe is expressed in differentiating and mature neurons, and its function is required for CNS regeneration. In this study, we show that coe is required to maintain structure and function of the CNS in uninjured planarians. We took advantage of this phenotype to identify genes regulated by coe by comparing global gene expression changes between control and coe mRNA-deficient planarians. This approach revealed downregulated genes downstream of coe with biological roles in CNS function. Expression analysis of the downregulated genes uncovered previously unknown candidate targets of coe in the CNS. Furthermore, functional analysis of downstream targets identified coe-regulated genes required for CNS repair. These results demonstrate that the roles of COE in stem cell specification and neuronal function are active and indispensable during CNS maintenance in adult animals.

Scientific Abstract:
Members of the COE family of transcription factors are required for central nervous system (CNS) development. However, the function of COE in the post-embryonic CNS remains largely unknown. An excellent model for investigating gene function in the adult CNS is the freshwater planarian. This animal is capable of regenerating neurons from an adult pluripotent stem cell population and regaining normal function. We previously showed that planarian coe is expressed in differentiating and mature neurons and that its function is required for proper CNS regeneration. Here, we show that coe is essential to maintain nervous system architecture and patterning in intact (uninjured) planarians. We took advantage of the robust phenotype in intact animals to investigate the genetic programs coe regulates in the CNS. We compared the transcriptional profiles of control and coe RNAi planarians using RNA sequencing and identified approximately 900 differentially expressed genes in coe knockdown animals, including 397 downregulated genes that were enriched for nervous system functional annotations. Next, we validated a subset of the downregulated transcripts by analyzing their expression in coe-deficient planarians and testing if the mRNAs could be detected in coe+ cells. These experiments revealed novel candidate targets of coe in the CNS such as ion channel, neuropeptide, and neurotransmitter genes. Finally, to determine if loss of any of the validated transcripts underscores the coe knockdown phenotype, we knocked down their expression by RNAi and uncovered a set of coe-regulated genes implicated in CNS regeneration and patterning, including orthologs of sodium channel alpha-subunit and pou4. Our study broadens the knowledge of gene expression programs regulated by COE that are required for maintenance of neural subtypes and nervous system architecture in adult animals.